UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/334,325	06/16/99	CEDERHOLM-WILLIAMS	S	CV0276A

HM22/0103

T R FURMAN
BRISTOL-MYERS SQUIBB COMPANY
100 HEADQUARTERS PARK DRIVE
SKILLMAN NJ 08558

EXAMINER	
CHEN, S	
ART UNIT	**PAPER NUMBER**
1633	5

DATE MAILED: 01/03/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev. 2/95)

1- File Copy

Office Action Summary

Application No.	Applicant(s)
09/334,325	Stewart Cederh Im-Williams
Examiner	**Group Art Unit**
Shin-Lin Chen	1633

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL**..

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 1-12 is/are pending in the applicat

Of the above, claim(s) 5-12 is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-4 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 4

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

This application claims the benefit of of provisional applications 60/083,571 filed 4-30-98 and 60/089,543 filed 6-17-98, and is a continuation of 09/303,377 filed 4-30-99.

Election/Restriction

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

   I. Claims 1-4, drawn to method of transforming a cell by applying nucleic acid and fibrin gel to the cells separately, or applying nucleic acid in admixture with fibrin or fibrinogen composition to the cells, and using the transformed cells for gene therapy (*ex vivo*), classified in class 435, subclass 455.

   II. Claims 5-8, drawn to method of conducting gene therapy by applying effective amount of nucleic acid and fibrin gel to the tissue of a subject *in vivo*, classified in class 514, subclass 44.

   III. Claims 9 and 10, drawn to a kit comprising compositions for forming fibrin gel and nucleic acid molecule, classifiable in class 536, subclass 23.1.

   IV. Claims 11 and 12, drawn to method of conducting gene therapy comprising transforming a cell with nucleic acid, and implanting the recombinant cells into an animal and applying fibrin gel to entrap the implanted recombinant cells within the animal (*ex vivo*), classified in class 424, subclass 93.2.

2. The inventions are distinct, each from the other because of the following reasons:

Groups I, II and IV are distinct form group III because I, II and IV are drawn to method for transforming a cell and method of gene therapy which is different from a kit for forming fibrin gel comprising fibrin monomer, fibrinogen, fibrin precursor, or fibrin-analog, the catalyst and nucleic acid molecule. The kit is primaily drawn to a fibrin composition, albrit part of methods claimed, it is considered distinct since the methods per se are drawn to using the fibrin gel with the fibrin materials as in the kit. Thus, each the kit and the methods would require separate scientific considerations and therefore different searches.

Group I is distinct from IV even though they both are drawn to *ex vivo* gene therapy, each uses different starting materials. Group I only uses recombinant cells for gene therapy, whereas, group IV use both recombinant cells and fibrin gel for gene therapy. They are different methods having different mechanisms because of the divergent starting materials. Thus, they are not obvious methods of each other and require a separate search based on their differing scientific consideration.

Group II is distinct from I and IV because II is drawn to *in vivo* gene therapy using nucleic acid and fibrin gel, whereas group I and IV are drawn to *ex vivo* gene therapy using recombinant cells and/or fibrin gel. They are different methods having different mechanisms because of the different starting materials and actual methods. One is *ex vivo* transformation and the other drawn to *in vivo*. Delivery issues differ scientifically, each require a separate search.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter and as shown by their different classification, restriction for examination purposes as indicated is proper.

During a telephone conversation with Mr. John Kilcoyne on 12-17-99 a provisional election was made without traverse to prosecute the invention of group I, claims 1-4. Affirmation of this election must be made by applicant in replying to this Office action. Claims 5-12 withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(I).

Priority

3. If applicant desires priority under 35 U.S.C. 119 (e) based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph.

An application in which the benefits of an earlier application, 09/303,377, are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

Double Patenting

4. Claims 1 and 2 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of copending Application No. 09/303,377. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1 and 2 of the present application are directed to a method of transforming a cell by applying nucleic acid and fibrin gel to the cells separately, or applying nucleic acid in admixture with fibrin or fibrinogen composition to the cells, whereas, claims 1-3 are drawn to the use of fibrin matrix for the enhancement of genetic transformation wherein said fibrin is autologous to the patient. Claims 1 and 2 of the present aplication do not teach fibrin to be autologous to the patient, however, it would have been obvious for a person of ordinary to use fibrin which is autologous to the patient for the purpose of reducing immune response of the patient to the fibrin. In addition, fibrin matrix and fibrin gel are same thing. Thus, claims 1 and 2 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of copending Application No. 09/303,377.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1 and 2 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1 and 2 are directed to a method of transforming a cell by applying nucleic acid and fibrin gel to the cells separately, or applying nucleic acid in admixture with fibrin or fibrinogen composition to the cells. Claims 1 and 2 encompass any vector or vehicle, and any nucleic acid for transforming a cell *in vitro* and *in vivo* at any location of any subject including human beings, mammals, fish, bird, insect, fungus, plant.

The specification discloses the preparation of preferred sealant compositions and the incorporation of nucleic acid into fibrin gel, but fails to provide an enabling disclosure for the method of using fibrin monomer or fibrinogen for genetic transformation of any gene in any type of cell or subject *in vitro* or *in vivo*, because the specification fails to provide sufficient guidance or demonstrate any data for the genetic transformation of any nucleic acid, DNA or RNA in any type of cell or subject *in vitro* or *in vivo* via fibrin gel. No teachings are present within the specification in regard to how to transform a cell with any nucleic acid in any vector or any

vehicle by using fibrin monomer or fibrinogen, how the nucleic acid entrapped in fibrin gel can be taken up by cells, or how to determine such cells are transformed with said nucleic acid.

The specification also fails to provide sufficient description of the vector or vehicle used in the method with fibrin monomer or fibrinogen for genetic transformation. No description of any vector suitable with fibrin as claimed is present in the as filed specification. Therefore the practitioner at the time of the invention would have been required to exercise undue experimentation to transform cells with nucleic acid and fibrin gel or the mixture of nucleic acid and fibrinogen composition and show the uptake of nucleic acid by the cells. Thus, claims 1 and 2 are rejected under 35 U.S.C. 112 first paragraph.

7. Claims 3 and 4 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 3 and 4 are directed to a method of conducting *ex vivo* gene therapy by implanting the transformed cells into an animal. Claim 4 specifies the use of a precursor cell and maturing the cell to a specialized cell type *in vitro* or *in vivo* following implanting. Claims 3 and 4 encompass gene therapy using any nucleic acid in any vector under the control of any promoter for the treatment of any disease or disorder in any subject including human beings, mammals, fish, bird, insect, fungus, plant, and also encompass any stem cells transformed *ex vivo* for gene therapy.

The specification fails to provide an enabling disclosure for gene therapy using any nucleic acid in any vector under the control of any promoter for the treatment of any disease or disorder in any subject including human beings, mammals, fish, bird, insect, fungus, plant. The specification fails to provide sufficient guidance or demonstrate any data of any therapeutic effect of any gene therapy using any recombinant cells, such as recombinant stem cells, which are transformed by nucleic acid in any vector under the control of any promoter for the treatment of any disease or disorder in any subject.

The specification does not disclose what type of nucleic acid is to be used for gene therapy, which nucleic acid is to be used for a specific type of disease or disorder, how and where the recombinant cells are to be administered to the subject, what type of disease related to said nucleic acid is to be treated and how to monitor the effect of the treatment on the subject. The scope of the invention encompasses any type of diseases or disorders and any recombinant cells which are transformed by any nucleic acid which might be related to said diseases or disorders, and it encompasses a very broad range of subject including plant, animal and human beings a very broad range of stem cells. It is unclear whether the application of the recombinant cells containing any recombinant nucleic acid will exhibit any therapeutic effect to each individual related disease or disorder of any subject.

The field of gene therapy at the time of the invention was unpredictable. For example, cystic fibrosis gene therapy using adenoviral vector, adenovirus genes express proteins that trigger immune responses and provoke inflammation along with an immune attack that

neutralizes cells containing adenovirus genes. When administered at low concentrations it is insufficient, but at high doses, it appears to cause acute inflammation (E. Marshal, 1995 (U)). Nabel et al., 1994 (V) indicates several issues relevant to the application of adenoviral vectors to human therapies need to be investigated, including stability of gene expression, host-cell immune response, transmission to germ-line cells, and toxicity (e.g. page 248, 249). The specification of the present application fails to provide adequate guidance and demonstrate data on how long can the recombinant cells survive after implantation, and how the intended therapeutic product being released to the target environment of a subject for a sufficient duration of time to exhibit therapeutic effect on the target cell or tissue, and therefore the practitioner would have been required to have exercised undue experimentation in the practice of the full scope of the claimed invention.

Bradley et al., 1992 (W) set forth the state of the art with respect to embryonal stem (ES) cells for species other than mice and the unpredictability of the non-human ES cells other than mice ES cells giving rise to somatic and germ cells. Bradley et al. disclose that at that time, there were no ES cells for any animal other than a mouse which had been established to rise to somatic tissues or germ cells *in vivo* (e.g. p. 537, 538). The claims encompass use of any transformed stem cells including human and all other types of stem cells, for gene therapy of any diseases or disorders in any subject including human beings, mammals, fish, bird, insect, fungus, plant, and if ES cells other than mouse ES cells have not been established at the time of filing, the transformation of these stem cells and the use of the transformed stem cells would be

unpredictable if not virtually impossible. In addition, the specification of the present application fails to provide adequate guidance and demonstrate data on how and where the recombinant stem cells are to be administered to the subject, how long the transformed stem cells will survive and whether they can differentiate into mature cell type after implantation into a subject, the selection a certain type of stem cells transformed with certain nucleic acid for a specific type of disease or disorder, and whether there is any therapeutic effect of using said stem cells on the subject. Thus, it is unpredictable at the time of the invention to produce transformed ES cells other than mouse ES cells and used said transformed ES cells for gene therapy of any diseases or disorders and exhibit any therapeutic effect in any subject. It is noted that the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991).

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to have made and used the claimed inventions. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the absence of working examples and scarcity of guidance in the specification, and the unpredictable nature of the art.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1 and 2 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: for example, how to determine the cells are transformed with nucleic acid.

10. Claims 3 and 4 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: for example, what type of transformed cells containing which recombinant nucleic acid are used, what kind of diseases or disorders are intended, and whether the implanted transformed cells are present long enough to secret therapeutic effective amount of therapeutic product into the implanted site to exhibit therapeutic effect on the subject.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

12. Claim 2 is rejected under 35 U.S.C. 102(e) as being anticipated by Donovan et al., US Patent No. 5,833,651, 1998 (A).

Claim 2 is directed to a method of transforming a cell by applying nucleic acid in admixture with fibrin or fibrinogen composition to the cells. Claim 2 encompass any vector or vehicle, and any nucleic acid for transforming a cell *in vitro* and *in vivo* at any location of any subject including human beings, mammals, fish, bird, insect, fungus, plant.

Donovan et al. constructed plasmid pCMVhpAP expressing the reporter hpAP gene under the control of CMV promoter and an E1 deleted recombinant adenoviral vector ADVhpAP expressing hpAP, and prepared a fibrin covered stent which was placed in a solution of plasmid or virus overnight to load the plasmid or virus into the fibrin covered stent for determining whether fibrin enhances gene delivery to the artery (e.g. column 18, 19, 20). Donovan et al. also teach mixing a solution of fibrin monomer and virus containing nucleic acid to form a polymer, i.e. fibrin gel, which can be used to deliver the virus to the cell *in vivo*, i.e. transformation of the cells (e.g. column 13). Thus, claim 2 is anticipated by Donovan et al..

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.

JOHN L. LeGUYADER
PRIMARY EXAMINER
GROUP 1800